Synthesis and Antiviral Activity of 5′-Deoxypyrazofurin

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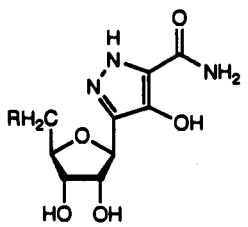
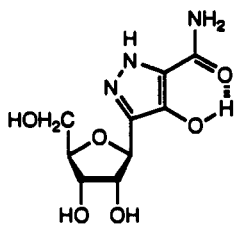
In searching for derivatives of pyrazofurin that could display antiviral properties by means that do not require C-5′ phosphorylation, 5′-deoxypyrazofurin (**3**) has been synthesized in six steps from methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**4**). Compound **3** was evaluated for antiviral activity against a large number of viruses including herpes-, pox-, myxo-, toga-, arena-, rhabdo-, picorna-, reo-, and retroviruses. Compound **3** proved active against respiratory syncytial virus (in HeLa cells), vaccinia virus (in embryonic skin–muscle fibroblast cells), vesicular stomatitis virus (in HeLa cells), and influenza A virus (in Madin–Darby canine kidney cells) at concentrations (ranging from 4 to 20 μg/mL) that were nontoxic to the confluent host cell cultures.

The range of antiviral potential for the C-nucleoside pyrazofurin (**1**) is impressive;[1,2] however, there have been reports[2a,3a] that toxicity may[3b] limit the usefulness of **1** as an antiviral agent. The lack of promising selectivity for **1** is likely tied to its intracellular conversion to the 5′-monophosphate,[4] which is the derivative responsible for both its antiviral properties and toxicity. We recently sought derivatives of **1** that would be incapable of undergoing phosphorylation with the intention that antiviral properties would result whose mechanism of action would not reside in a need to undergo phosphorylation.[5] For example, as a result of the ability of **1** to adopt the adenosine-like structure **2** through intramolecular hydrogen bonding,[6] inhibition of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase[7] could result. To address this possibility, 5′-deoxypyrazofurin (**3**)[8] has been prepared and evaluated.



1, R=OH
3, R=H



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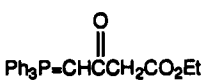

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Chemistry

Using an adaptation of a reported preparation of pyrazofurin,[9] the synthesis of **3** began with the conversion of methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (**4**)[10] into 5-deoxy-2,3-(di-*O*-benzyl)-D-ribofuranose (**5**) as shown in Scheme I. Treatment of **5** with the ylide [3-(ethoxycarbonyl)-2-oxopropylidene]triphenylphosphorane (**6**)[11] provided ethyl 3-oxo-4-[5′-deoxy-2′,3′-(di-*O*-benzyl)-α- and -β-D-ribofuranosyl]butanoate (**7**) that was, in turn, converted into the diazo ketone **8** upon reaction with *p*-toluenesulfonyl azide in the presence of triethylamine. Ring closure of **8** using sodium hydride produced ethyl 4-hydroxy-3(5)-[5′-deoxy-2′,3′-(di-*O*-benzyl)-α- and -β-D-ribofuranosyl]pyrazole-5(3)-carboxylate (**9**). Ammonolysis of **9** yielded 4-hydroxy-3(5)-[5′-deoxy-2′,3′-(di-*O*-benzyl)-β-D-ribofuranosyl]pyrazole-5(3)-carboxamide (**10**) in the desired anomerically pure β-form.[9] Debenzylation of **10** gave the desired **3**.

Antiviral Results

Compound **3** was evaluated against a wide variety of both DNA viruses and RNA viruses (Table I). Cytotoxicity for uninfected host cells was determined under the same conditions as antiviral activity (*i.e.*, microscopic evaluation of cell morphology of confluent cell monolayers or inhibition of cell growth which had or had not been inoculated with virus). The greatest activity with compound **3** was noted against RSV (IC_{50}: 4 μg/mL) and VV (IC_{50}: 5.5 μg/mL). The activity for **3** against RSV was comparable to that of ribavirin. Toxicity of **3** to the host cells did not appear up to concentrations of 400 μg/mL for ESM and Vero cells and 170 μg/mL for HeLa cells. This means that its selectivity index was ≥43 for RSV (in HeLa cells) and ≥73 for VV (in ESM cells). Compound **3** showed some activity against VSV (in HeLa cells) and influenza A (in MDCK cells) at an IC_{50} of 14 and 20 μg/mL, respectively. Compound **3** exhibited little, if any, inhibitory activity against HSV-1, HSV-2, VZV, CMV, influenza B, Coxsackie B4, polio-1, PV-3, SV, SFV, Reo-1, JV, and TV. It was also inactive against HIV-1 and HIV-2 in MT-4 cells at the highest concentrations that could be evaluated (4 μg/mL). At higher concentrations, it proved toxic to the growth of the host cells.

The mechanism of action of compound **3** remains the subject of further study. Compound **3** showed activity against VV, RSV, and VSV (*i.e.*, three viruses that fall within the activity spectrum of the AdoHcy hydrolase inhibitors[7]). However, it was not active against other viruses (*i.e.*, PV-3, JV, TV, and Reo-1) that also fall within the purview of the AdoHcy hydrolase inhibitors. Although other molecular targets for the antiviral action of **3** cannot be excluded, it is possible that it interacts with AdoHcy

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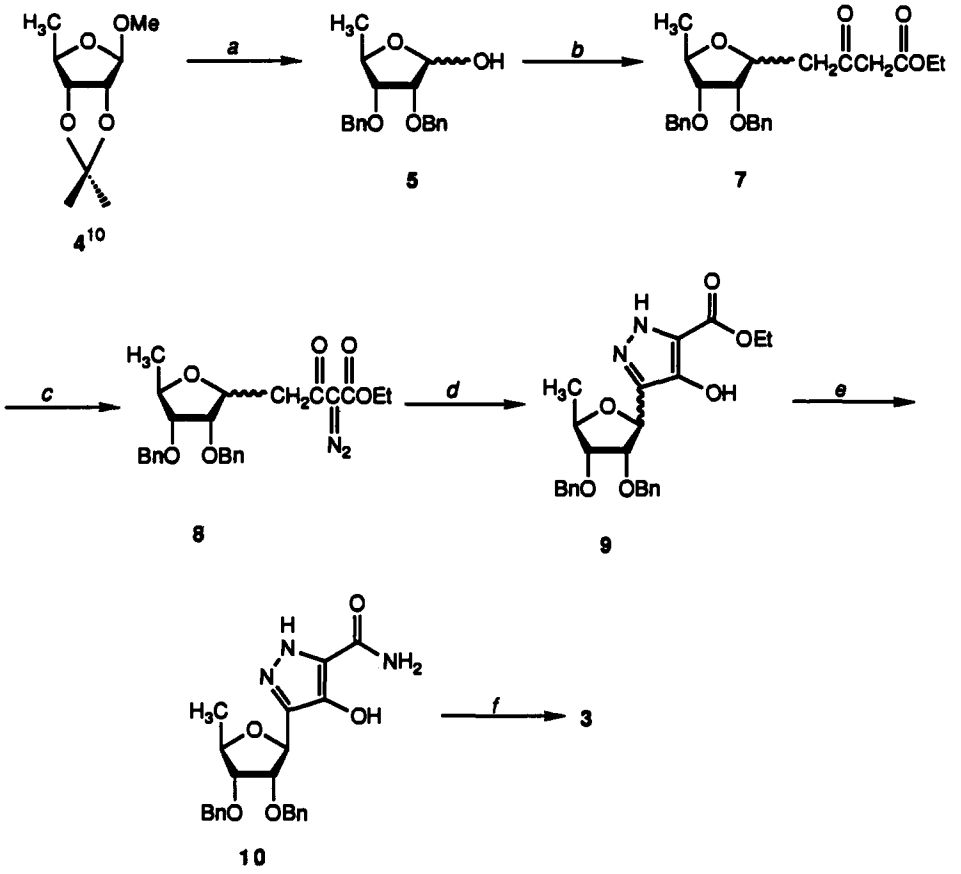
Scheme I[a]



[a] Reaction conditions: (a) (i) H^+ resin in MeOH, reflux; (ii) NaH and BnBr in DMF, 0 °C; (iii) 1 N HCl in dioxane, reflux; (b) 6[11] in MeCN, reflux; (c) *p*-TsN_3 and Et_3N in MeCN, 15 °C; (d) NaH in THF; (e) NH_3 in MeOH, 90–95 °C; (f) H_2/10% Pd–C in MeOH.

hydrolase in such a way that it shows up only with some viruses but not others. This hypothesis could be substantiated only by identification of other AdoHcy hydrolase inhibitors with a similar antiviral activity spectrum.

Experimental Section

Materials and Methods. Melting points were recorded on a Mel-Temp capillary melting point apparatus and are uncorrected. The microanalysis was performed by M-H-W Laboratories, Phoenix, AZ. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer (operated at 90 and 22.5 MHz, respectively) in $CDCl_3$ or DMSO-d_6 referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck silica gel 60-F_{254} precoated silica gel plates with visualization by irradiation with a Mineralight UVGL-25 lamp or exposure to iodine vapor. The column chromatographic purifications were performed using Davidson Chemical silica gel (60–200 mesh) or Aldrich silica gel (230–400 mesh, 60 Å) and eluting with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials. The reactions were generally carried out in a N_2 atmosphere under anhydrous conditions.

4-Hydroxy-3(5)-(5′-deoxy-β-D-ribofuranosyl)pyrazole-5(3)-carboxamide (5′-Deoxypyrazofurin, 3). To a solution of methyl 5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside (4)[10] (40 g, 0.21 mol) in MeOH (500 mL) was added Amberlite IR-120 (H^+) ion exchange resin (400 g) that had been pre-equilibrated several times with absolute MeOH. The mixture was stirred and heated under reflux for 4 h, cooled to room temperature, and filtered. The resin was washed with MeOH. The original filtrate and the washings were combined and evaporated to dryness. The residual syrup (21 g, 0.14 mol) dissolved in dry DMF (150 mL) was added to a suspension of NaH (10 g, 0.33 mol, 80% in oil) in dry DMF (100 mL). To this DMF solution was added benzyl bromide (55 g, 0.32 mol) at 0 °C. The resultant reaction mixture was stirred for 5 h, which was followed by the careful addition of H_2O at 0 °C. Ethyl ether (300 mL) was added and the ether layer separated and washed with H_2O (5 x 100 mL). The ether layer was then dried (Na_2SO_4) and evaporated. The residual material was dissolved in a mixture of dioxane (300 mL) and 1 N HCl (100 mL), and the solution that resulted was refluxed for 6 h. After removal of the dioxane by rotary evaporation, Et_2O was added and the resultant mixture was washed with H_2O. The ether layer was dried (Na_2SO_4) and evaporated. The residual material was subjected to column chromatography with hexane–AcOEt (5:1) to give 5-deoxy-2,3-(di-*O*-benzyl)-D-ribofuranose (5) (17 g, 38%) as a syrup: ^1H NMR ($CDCl_3$) δ 1.15 and 1.3 (dd, J = 12 Hz, 3 H, CH_3 of α/β mixture), 3.50–4.40 (m, 3 H, H-2, H-3, and H-4), 4.45–4.70 (4 s, 4 H, PhCH_2 of α/β mixture), 5.13 (dd, 1 H, H-1 of α/β mixture), 7.32 (m, 10 H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 19.5 and 20.5 (CH_3 of α/β mixture), 72.0, 72.3 and 72.5 (PhCH_2 of α/β mixture), 77.0, 80.5 and 81.7, 81.7 and 82.5 (C-2, C-3, and C-4 of α/β mixture), 90.5 and 100.0 (C-1 of α/β mixture), 127.0–129.0 and 137.2–138.0 (Ar).

A solution of 5 (17 g, 54 mmol) and [3-(ethoxycarbonyl)-2-oxopropylidene]triphenylphosphorane (6)[11] (63 g, 128 mmol) in anhydrous MeCN (100 mL) was refluxed for 48 h. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography purification. Elution with hexane–AcOEt (5:1) gave ethyl 3-oxo-4-[5′-deoxy-2′,3′-(di-*O*-benzyl)-α- and -β-D-ribofuranosyl]butanoate (7) (16.6 g, 72%) as a viscous oil: ^1H NMR ($CDCl_3$) δ 1.05–1.35 (m, 6 H, CH_2CH_3 and 5′-CH_3), 2.50–3.0 (m, 2 H, H-4), 3.30–4.30 (m, 8 H, CH_2CH_3, H-2, H-1′, H-2′, H-3′, and H-4′), 4.45–4.65 (m, 4 H, 2 × PhCH_2), 7.30 (m, 10 H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 16.0 (CH_2CH_3), 21.5 and 21.8 (5′-CH_3 of α/β mixture), 45.5 and 45.8 (C-4 of α/β mixture), 51.5 (C-2), 63.0 (CH_2CH_3), 73.5, 74.5 and 75.5 (2 × PhCH_2 of α/β mixture), 77.2 and 77.8, 79.0 and 79.8, 81.5 and 81.9, 84.6 and 86.2 (C-1′, C-2′, C-3′, and C-4′ of α/β mixture), 128.5–131.5 and

Table I. Inhibitory Effects of 5′-Deoxypyrazofurin (3) on Virus Replication in Various Assay Systems

virus	cell	IC_{50} (μg/mL)[a] 3	ribavirin	DHPA	ACV
		DNA Viruses			
HSV-1 (KOS)	ESM	≥350	≥350	≥220	
HSV-2 (G)	ESM	>300	>300	>300	
TK⁻ HSV-1 (B2006)	ESM	55	≥135	≥300	
TK⁻ HSV-1 (VMW 1837)	ESM	70	110	≥205	
VZV (Oka)	HEL	40			0.1
VZV (YS)	HEL	22			0.1
TK⁻ VZV (07/1)	HEL	>40			4
TK⁻ VZV (YS/R)	HEL	>40			5
CMV (AD-169)	HEL	>40		1.5	26
CMV (Davis)	HEL	>40		0.7	22
VV	ESM	5.5	45	11	
		RNA Viruses			
Influenza A	MDCK	20	4		
Influenza B	MDCK	>100	4		
RSV	HeLa	4	4		
PV-3	Vero	>200	20	80	
SV	Vero	>200	≥250	≥235	
SFV	Vero	>200	≥235	>400	
Coxsackie B4	Vero	70	20	>400	
Polio-1	HeLa	55	70	>400	
VSV	HeLa	14	14	45	
Reo-1	Vero	>175	160	55	
JV	Vero	>40	5.2		
TV	Vero	>40	6.4		
HIV-1	MT-4	>4	>5		
HIV-2	MT-4	>4	>5		
cell morphology	ESM	≥400	≥400	≥400	
	HeLa	≥170	≥400	>400	
	MDCK	100	>200	>200	
	Vero	>400	>400	>400	
cell growth	HEL	>50		>200	>200
	MT-4	8.8	6.5		>100
	L1210	37	7.1		
	FM3A	39	3.9		
	CEM	>49	19		

[a] 50% inhibitory concentration, required to reduce virus cytopathicity or virus plaque formation (VZV, CMV) or cell growth by 50%. Virus input was 100 $CCID_{50}$ (50% cell culture infectious dose) in the virus-induced cytopathicity assay and 100 PFU (plaque-forming units) in the virus plaque formation assay. For cell morphology, the IC_{50} corresponds to the lowest concentration required to cause a microscopically detectable alteration of normal cell morphology. For abbreviations, see the Experimental Section.

139.0–140.5 (Ar), 168.5 (ester carbonyl), 202.5 and 208.0 (ketone carbonyl of α/β mixture).

Triethylamine (3.9 g, 39 mmol) and *p*-toluenesulfonyl azide (17 mL) were added to a solution of **6** (16.6 g, 39 mmol) in anhydrous MeCN (140 mL). The mixture was kept at 15 °C for 30 min. The solvent was then evaporated under reduced pressure, and the residue was subjected to column chromatographic purification. Elution with hexane–AcOEt (5:1) gave ethyl 2-diazo-3-oxo-4-[5′-deoxy-2′,3′-(di-*O*-benzyl)-α- and -β-D-ribofuranosyl)-butanoate (**8**) as a viscous oil (8.5 g, 48%): ^{1}H NMR ($CDCl_3$) δ 1.10–1.35 (m, 6 H, CH_2CH_3 and C-5′ CH_3), 3.10–3.30 (m, 2 H, H-4), 3.50–4.50 (m, 5 H, CH_3CH_2, H-2′, H-3′, and H-4′), 4.60 (m, 4 H, 2 × $PhCH_2$), 4.85 (m, 1 H, H-1′), 7.30 (s, 10 H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 15.5 (CH_2CH_3), 20.2 and 20.7 (C-5′ CH_3 of α/β mixture), 45.5 (C-4′), 72.5 and 73.0 (2 × $PhCH_2$), 76.0, 77.7, 79.0, 80.5 and 82.5 (C-1′, C-2′, C-3′, C-2, and C-4), 127.0–130.0 and 137.5–138.5 (Ar), 161.5 (ester carbonyl), 189.5 and 191.0 (ketone carbonyl of α/β mixture).

A solution of **8** (8.5 g, 18.8 mmol) in dry THF (50 mL) was added dropwise to a stirred, ice-cooled suspension of NaH (3 g, 0.1 mol, 80% in oil) in dry THF (50 mL) under N_2. The mixture was stirred at room temperature for 24 h. A solution of AcOH (1.26 g, 21 mmol) in THF was then added dropwise to the stirred, ice cooled reaction mixture. The solvent was evaporated under reduced pressure to give a residue to which H_2O and Et_2O were added. The ether layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resultant residue was subjected to column chromatography using hexane–AcOEt (3:1) as the eluting solvent mixture to give ethyl 4-hydroxy-3(5)-[5′-deoxy-2′,3′-(di-*O*-benzyl)-α- and -β-D-ribofuranosyl]pyrazole-5(3)-carboxylate (**9**) (α/β = 1:1) as a foam (4.5 g, 53%): ^{1}H NMR ($CDCl_3$) δ 1.15–1.40 (m, 6 H, 2 × CH_3), 3.80 (q, 1 H, H-4′), 3.90–4.40 (m, 4 H, H-2′, H-3′, and CH_2CH_3), 4.35 and 4.60 (m, 4 H, 2 × $PhCH_2$), 5.20 and 5.32 (dd, 1 H, H-1′ of α/β mixture), 7.28 (m, 10 H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 13.2 (CH_2CH_3), 18.0 and 18.4 (C-5′ of α/β mixture), 60.0 and 60.3 (CH_2CH_3 of α/β mixture), 71.1 and 71.4, 71.8 and 72.2 (2 x $PhCH_2$ of α/β mixture), 76.0 and 76.5, 76.5 and 76.8, 77.5 and 78.5, 81.8 and 82.5 (C-1′, C-2′, C-3′ and C-4′ of α/β mixture), 122.0, 125.5, 132.0, 142.0 and 142.8 (C-3, C-4 and C-5 of α/β mixture), 127.2, 136.2 and 136.8 (Ar), 161.0 and 162.7 (carbonyl of α/β mixture).

A solution of α/β **9** (1.63 g, 3.6 mmol) in dry MeOH (30 mL) was saturated with anhydrous NH_3 at 0 °C. The solution was heated at 90–95 °C in a sealed vessel for 7 h. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography. Elution with hexane–AcOEt (3:1) gave 4-hydroxy-3(5)-[5′-deoxy-2′,3′-(di-*O*-benzyl)-β-D-ribofuranosyl]pyrazole-5(3)-carboxamide (**10**) (1.0 g, 66%, only β anomer) as a foam: ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 3 H, 5′-CH_3), 3.68 (m, 1 H, H-4′), 4.20–4.50 (m, 2 H, H-2′ and H-3′), 4.55 and 4.70 (2 s, 4 H, 2 × $PhCH_2$), 5.30 (d, 1 H, H-1′), 7.30 (m, 10 H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 18.9 (5′-CH_3), 71.9 (2 × $PhCH_2$), 76.8, 77.4, 79.5 and 82.2 (C-1′, C-2′, C-3′ and C-4′), 123.0, 130.0 and 140.5 (C-3, C-4 and C-5), 126.0–128.5, 137.1, and 137.3 (Ar), 165.8 (carbonyl).

A suspension of **10** (900 mg, 2.1 mmol) in MeOH (50 mL) containing 10% Pd–C (30 mg) was subjected to a pressure of H_2 (60 psi) for 2 days. Filtration of the suspension and evaporation of the filtrate gave a residue that was purified by column chromatography using CH_2Cl_2–MeOH (20:1) to give **3** (500 mg, 90%) as a white crystalline solid: mp 175–176 °C; ^{1}H NMR (DMSO-d_6) δ 1.20 (d, 3 H, CH_3), 3.70 (m, 2 H), 4.25 (t, 1 H), 4.67 (d, 1 H), 7.35 (s, 2 H, NH_2); ^{13}C NMR (DMSO-d_6) δ 19.0 (C-5′), 73.0 (ribofuranosyl C), 76.0 (2 × ribofuranosyl C), 78.5 (ribofuranosyl C), 127.5, 132.5, and 140.7 (pyrazole C), 163.5 (amide carbonyl). Anal. ($C_9H_{13}N_3O_5$).

Antiviral Activity Assays. Antiviral assays (except for the anti-VZV assays) were carried out as recently described.[12] For the anti-VZV assays, see ref 13. The sources of the viruses have also been described in these previous publications. The abbreviations used for the viruses and cells are as follows: HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; VZV, varicella-zoster virus; CMV, cytomegalovirus; VV, vaccinia virus; TK⁻, thymidine kinase deficient strains of HSV-1 or VZV; SV, Sindbis virus; SFV, Semliki forest virus; JV, Junin virus; TV, Tacaribe virus; RSV, respiratory syncytial virus; PV, parainfluenza virus; VSV, vesicular stomatitis virus; HIV-1, human immunodeficiency virus type 1; HIV-2, human immunodeficiency virus type 2; HEL, human embryonic lung; ESM, embryonic skin–muscle fibroblast; MDCK, Madin–Darby canine kidney.

Cytotoxicity Assays. Cytotoxicity measurements were based on microscopically visible alteration of normal cell morphology or inhibition of cell growth. The detailed methodology has been previously described.[12,14]

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